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(54) **Composite surgical material.**

(57) A composite surgical material comprising a collagen matrix reinforced by a layer of a synthetic bioabsorbable material such as polylactide/polyglycolide or oxidised regenerated cellulose, and wherein oil droplets are dispersed in the collagen matrix. The oil droplets comprise 1% to 75% of the weight of the composite and result in improved leak-proofing of the composite. The composite, in the form of a sheet or a tube, is especially useful as a temporary, fully bioabsorbable prosthesis, for membranes or blood vessels where a highly leak-proof prosthesis is required. The invention also provides a method of making a composite surgical material comprising the steps of : providing a layer of a synthetic bioabsorbable material ; providing a dispersion of collagen in an oil-in-water emulsion ; coating at least one face of the layer of synthetic bioabsorbable material with the said dispersion ; and drying the composite material thus obtained.

FIGURE 2

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The present inv nti n relates to bioabsorbable composite surgical materials, process s for their preparation and also the use of such materials for the preparation of surgical prosthes s and the like.

The us of bioabsorbabl materials (also called resorbabl materials or absorbabl materials) in surgery is by now quit well known. Th materials underg gradual degradation when they are introduced int th human or animal body. This degradation results from hydrolysis which takes place on contact with living tissue in the presence of proteolytic enzymes contained therein. The hydrolysis fragments from the hydrolysis of the bioabsorbable materials are non-toxic and readily absorbed by the human or animal body.

For example, bioabsorbable surgical sutures made from copolymers of lactic and glycolic acids are in widespread use. Such sutures do not need to be removed from the wound site after wound healing is complete. Instead, the sutures undergo slow hydrolysis and absorption by the body.

Other bioabsorbable surgical materials have been used as temporary prostheses in repair surgery. For example, sheets of bioabsorbable material may be used as prostheses for regions of the pericardium or the peritoneal membrane. Healing of the damaged membrane takes place from the edges of the prosthesis, and the prosthesis is gradually absorbed as healing progresses.

Likewise, tubes of bioabsorbable surgical material have been used as arterial grafts. Once again, healing of the damaged artery is accompanied by gradual resorption of the graft.

EP-A-0194192 describes a bioabsorbable composite material that is especially suitable for use as a surgical prosthesis. The material comprises a sheet of reconstituted collagen reinforced with a mesh of a synthetic bioabsorbable polymer such as polylactic/polyglycolic acid or oxidised regenerated cellulose. The composite material is sufficiently strong to be used as an arterial graft or the like, and in particular is strong enough to hold sutures. The reconstituted collagen sheet fills all of the interstices in the mesh and renders the composite material leak-proof. The leak-proofing effect is especially important when the material is to be used to repair blood vessels. Furthermore, it has been found that the reinforced collagen films are absorbed more slowly *in vivo* than non-reinforced collagen films.

A defect of the reinforced collagen films described in EP-A-0194192 is that the film does not remain leak-proof in use for a sufficiently long time to be usable for some surgical applications. This is to say, the rate of bioabsorption of the collagen is sufficiently rapid that in some cases the film may start to leak through the interstices of the reinforcing mesh before wound healing is complete.

The rate of absorption of collagen *in vivo* can be reduced by chemical cross-linking of the collagen with succinimide or glutaraldehyde. However, such chemical treatment necessarily renders the collagen less biocompatible.

It has now been found that reinforced collagen films similar to those described in EP-A-0194192 may be made with significantly improved leak-proofing characteristics by incorporating oil droplets into the collagen layer.

The present invention provides a composite surgical material comprising a collagen matrix reinforced by a layer of a synthetic bioabsorbable material and having oil droplets dispersed in the collagen matrix.

Preferably, the oil droplets comprise from 2% to 75% by weight of the composite material, more preferably from 5% to 50% by weight of the composite material, and most preferably from 10% to 40% by weight of the composite material.

The oil droplets are preferably microdroplets such that at least 90% of the droplets have diameters in the range 0.1μm to 250μm. More preferably, at least 90% of the droplets have diameters in the range 1μm to 50μm.

The oil droplets are preferably distributed uniformly throughout the collagen matrix. However, in certain embodiments, the oil droplets may be distributed non-uniformly, for example to provide different rates of bioabsorption of the collagen matrix in different regions of the composite material.

The oil may be any bioabsorbable and biocompatible oil. For example, vegetable oils such as corn oil, sunflower seed oil, sesame seed oil or linseed oil may be used. The term "oil" also encompasses oleaginous materials, such as lanolin, that are solid or semisolid at room temperature.

The collagen matrix preferably comprises insoluble fibrous collagen, such as insoluble Type I and/or Type III collagen fibres. The collagen matrix may additionally comprise soluble collagen, such as gelatin or atelocollagen, or acid - soluble collagen, or even collagen fibres reconstituted from these soluble collagens. The collagen may be obtained from any animal, fish or avian source, but is preferably obtained from bovine corium.

The relative amounts of the collagen matrix and the synthetic bioabsorbable material in the composite surgical materials according to the present invention may vary widely, depending on the intended use of the materials and the desired rate of bioabsorption. The composite materials preferably contain from 10% to 95% by weight of the collagen matrix (including the oil droplets and any other substances dispersed therein). Preferably, th composite materials contain from 20% to 60% by weight of the collagen matrix.

The reinforcing lay r is f rmed from a synthetic bioabsorbabl material. Preferred synthetic bioabsorbabl materials include synth tic suture materials such as polym rs or copolymers of lactic and/or glycolic acids.

Other pref rred synth tic bioabsorbable materials include modifi d celluloses, such as xidised regenerated cellul s . Particularly preferred synthetic bioabsorbable materials includ the polylactic/polyglycolic acid copolym r sold under th Register d Trade Mark VICRYL and th oxidised reg nerat d cellulos sold under the Regist red Trad Mark SURGICEL.

Th layer of synthetic bioabsorbable material is preferably in the form of a knitted, woven or non-woven mesh or web. This arrangement combines flexibility with sufficient strength for the composite material to hold sutures. The foraminous nature of these reinforcing layers also assists suturing. The mesh size selected for the layer of synthetic bioabsorbable material can very widely, depending on the particular surgical application that is envisaged.

The composite surgical materials according to the present invention preferably further comprise pharmacologically active agents dispersed in the collagen matrix. Preferred pharmacologically active agents include antibiotics, antiseptics, anti-inflammatory agents and agents that promote wound healing, such as cytokines or glycosaminoglycans (e.g. hyaluronic acid and its salts, heparin and the like). The pharmacologically active agents are preferably present in an amount of 0.01%-5% by weight, more preferably 0.01%-1% by weight based on the total weight of the composite material. It will be appreciated that the presence of the oil droplets allows oleophilic active agents to be dispersed in the collagen matrix as well as hydrophilic active agents.

The composite surgical materials according to the present invention are preferably in the form of a flat sheet or a tube.

The present invention also encompasses the use of the above composite surgical materials for the preparation of a bioabsorbable surgical graft or prosthesis. For example, flat sheets of the material according to the present invention may be used as membrane grafts for repair of the peritoneum or pericardium. Tubes of the material according to the present invention may be used as grafts for the repair of blood vessels. It has been found, surprisingly, that the sheets and tubes of material according to the present invention remain leak-proof for substantially longer than corresponding materials prepared in accordance with EP-A-0194192.

The present invention also provides a process to prepare a composite surgical material comprising the steps of: providing a layer of a synthetic bioabsorbable material; providing a dispersion of collagen in an oil-in-water emulsion; coating at least one face of the layer of synthetic bioabsorbable material with the said dispersion; and drying the composite material thus obtained.

Preferably, the step of providing a dispersion of collagen in an oil-in-water emulsion comprises adding the collagen and the oil to water followed by emulsifying the oil at high shear. Emulsifiers may be added to assist this process, but are not always necessary, since collagen is an effective emulsifier. Where the oil is a solid or semisolid oleaginous material at room temperature (e.g. lanolin), the emulsification step is carried out at an elevated temperature, at which the oil is liquid.

Preferably, the weight ratio of collagen to oil in the emulsion is from 10:1 to 1:10, more preferably is from 2:1 to 1:5, and most preferably it is from 1:1 to 1:3. Preferably, the concentration of collagen in the emulsion is from 0.05% w/v to 10% w/v, more preferably 0.1% w/v to 5% w/v.

Preferably, the collagen, oil and synthetic bioabsorbable polymer are as defined above for the preferred embodiments of the composite surgical material according to the present invention.

Specific embodiments of the present invention will now be described further, by way of example, with reference to the accompanying Figures, in which:

Figure 1 shows a photomicrograph of a cross section through a collagen/vicryl film subcutaneous inplant after 14 days; and

Figure 2 shows a photomicrograph of a cross section through a collagen/oil/vicryl film subcutaneous inplant (500% oil/collagen w/w) after 14 days.

Example 1

Reinforced collagen films according to the present invention are prepared as follows.

Fibrous collagen obtained from bovine corium, prewashed to remove the majority of non-collagenous components as described in US-A-4614794 or US-A-4320201 is suspended in clear, deionised pyrogen-free water and homogenised to a fine fibrous suspension by passage through a homogenising system, such as that described in US-A-4320201. The collagen suspension is then acidified by addition of acetic acid at a concentration of 0.05M. The concentration of collagen fibres in the dispersion is 0.5% w/v.

To this suspension is added sesame seed oil at 50%, 100%, 200%, or 500% (as % of the collagen content, w/w). The mixture is homogenised t form an emulsi n, degassed under vacuum, and poured into trays. In th trays a m sh of poly(L-lactide) p ly(L-glycolid) (supplied by Ethicon Inc. und r th Registered Trad Mark VICRYL, styl 9) is immersed in th collagen/oil mulsi n. Th mulsi ns are dried in air at room temperature t form films.

F r comparison purpos s a film was made in identical fashion, but with zero il cont nt.

Example 2

The permeability to physiological saline of films prepared in accordance with Example 1 is determined as follows.

Pieces of collagen/oil/Vicryl™ film (oil content with respect to collagen: 0 (comparative example), 50%, 200%, 500%) are clamped between two hollow, flanged, cylindrical chambers (2.5cm diameter) to form a watertight seal. This apparatus is suspended vertically over a beaker in a humidified chamber at 37°C. 25 ml of phosphate-buffered saline is placed in the upper chamber. The volume permeating through the film is collected in the beaker and measured daily, at which time the volume of saline in the upper chamber is replenished to 25ml.

The results are expressed as the cumulated volume of saline which has passed through the films. During the first 9 days there is no significant difference in permeability between the different films. However, from days 10 to 17 there is a significant variation in permeability which correlates with the oil content of the films:

Oil content (%)	vol.(ml)days 1-9	vol.(ml)days 10-17
0 (comparative)	81	137
50	70	106
200	74	101
500	82	82

Example 3

The effect of oil content on the susceptibility of reinforced collagen films to degradation by collagenase is determined as follows.

Pieces of film prepared as in Example 1 are cut to give a collagen content of approx. 50mg. These are incubated at 37°C in 32.5 ml of Tris buffer (pH7.2) containing bacterial collagenase (Clostridiopeptidase A) at 50 U/ml for 2.5h. collagen degradation is measured by hydroxyproline assay of aliquots of the supernatant solution after centrifugation, and expressed as a % of the starting collagen content of the sample.

Collagen degradation was significantly decreased in films containing oil at 200% and 500% of the weight of collagen (degradation: 63.9% and 49.2%, respectively, compared with 85.0% degradation of collagen film containing no oil).

Example 4

The effect of oil content on the susceptibility of reinforced collagen films to degradation *in vivo* is determined as follows.

Pieces of film (0.5cm x 1cm) prepared as in Example 1 are implanted subcutaneously in 10wk old Wistar rats, which are sacrificed at 7 and 14 days. The implant and surrounding tissue are excised, fixed, paraffin-wax embedded, sectioned and stained with haematoxylin/eosin. All the films containing oil have retained their integrity and showed significantly less degradation than those without oil at both time-points. This is illustrated in the Figures, in which the remaining reinforced collagen film after 14 days is labelled C. The oil-free film in Figure 1 (comparative example) clearly shows more degradation than the film according to the present invention shown in Figure 2.

The above embodiments have been described by way of example only. Many other embodiments falling within the scope of the accompanying claims will be apparent to the skilled reader.

Claims

1. A composite surgical material comprising a collagen matrix reinforced by a lay r of a synthetic bioabsorbable material and having oil dropl ts disp rsed in th collag n matrix.

2. A composite surgical material according t claim 1, wherein the il droplets comprise from 1% to 75% by

w ight of th composite surgical material.

3. A composite surgical material according t claim 1 or 2, wherein the oil droplets comprise from 5% to 50% by weight of th composite surgical material.

4. A composite surgical material according to any preceding claim, wherein the oil droplets comprise from 10% to 40% by weight of the composite surgical material.

5. A composite surgical material according to any preceding claim wherein the synthetic bioabsorbable material comprises a polymer or copolymer of lactic acid and/or glycolic acid.

6. A composite surgical material according to any preceding claim wherein the synthetic bioabsorbable material comprises oxidised regenerated cellulose.

7. A composite surgical material according to any preceding claim wherein the layer of synthetic bioabsorbable material is a knitted, woven or non-woven mesh or web.

8. A composite surgical material according to any preceding claim, further comprising an antibiotic, an antiseptic or an anti-inflammatory.

9. A composite surgical material according to any preceding claim further comprising a growth factor, a cytokine or a glycosaminoglycan.

10. A composite surgical material according to any preceding claim which is in the form of a sheet or a tube.

11. Use of a composite surgical material according to any preceding claim for the preparation of a surgical graft or prosthesis.

12. A process to prepare a composite surgical material comprising the steps of:
providing a layer of a synthetic bioabsorbable material;
providing a dispersion of collagen in an oil-in-water emulsion;
coating at least one face of the layer of synthetic bioabsorbable material with the said dispersion; and
drying the composite material thus obtained.

13. A process according to claim 12 wherein the step of providing a dispersion of collagen in an oil-in-water emulsion comprises mixing the collagen and the oil with water followed by emulsifying the oil.

14. A process according to claim 12 or 13, wherein the collagen comprises insoluble fibrous collagen.

15. A process according to claim 12, 13 or 14, wherein the weight ratio of collagen to oil in the said emulsion is from 10:1 to 1:10.

16. A process according to claim 15, wherein the weight ratio of collagen to oil in the said emulsion is from 2:1 to 1:5.

17. A process according to claim 16, wherein the weight ratio of collagen to oil in the said emulsion is from 1:1 to 1:3.

18. A process according to any of claims 12 to 17, wherein the synthetic bioabsorbable material comprises a polymer or copolymer of lactic acid and/or glycolic acid.

19. A process according to any of claims 12 to 18, wherein the synthetic bioabsorbable material comprises oxidised regenerated cellulose.

20. A process according to any of claims 12 to 19, wherein the layer of synthetic bioabsorbable is a knitted, woven or non-woven mesh or web.

21. A process according t any f claims 12 to 20, further comprising the step f dispersing an antibiotic, an antiseptic or an anti-inflammatory compound in th said il-in-water emulsion.

22. A process according to any of claims 12 t 21, further comprising th step of dispersing a growth factor, a cytokine and/or a glycosamin glycan in the said il-in-water emulsion.

FIGURE 1

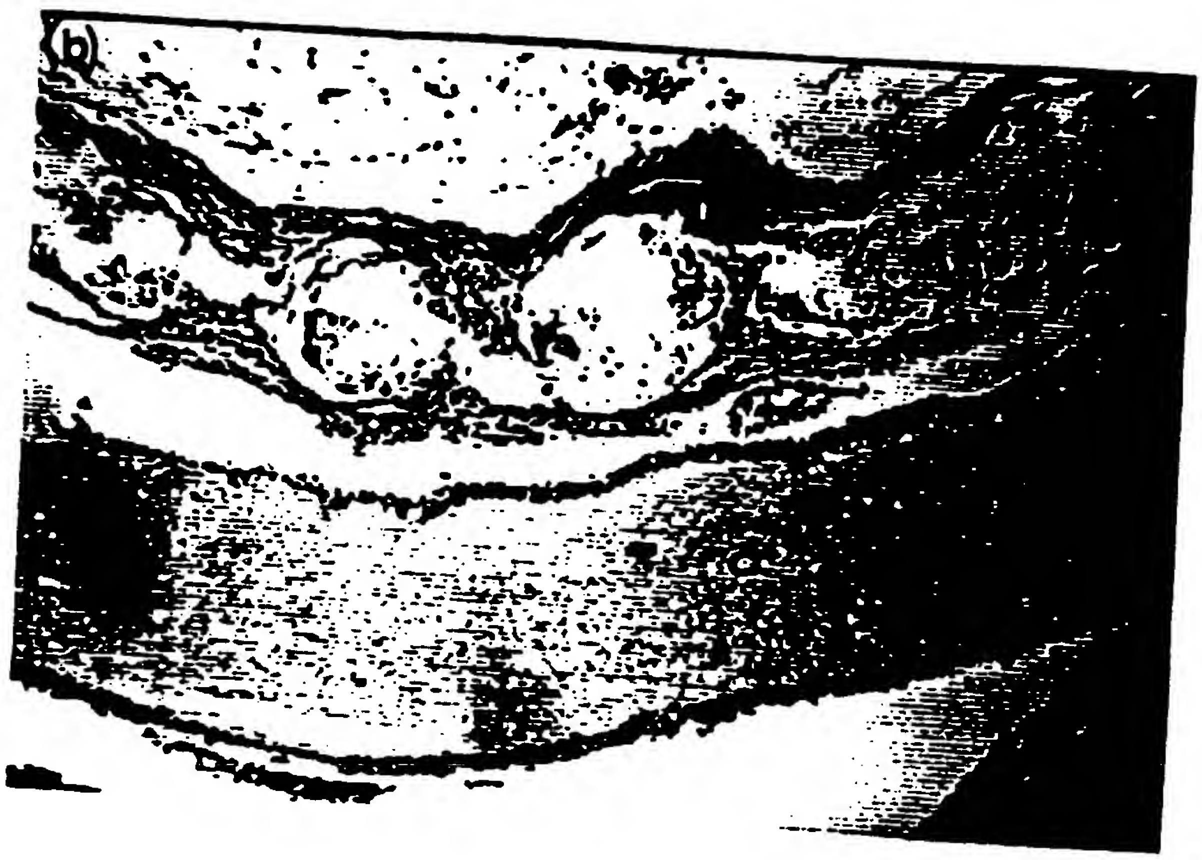

FIGURE 2

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EUROPEAN SEARCH REPORT

Application Number
EP 94 30 5536

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
X,P	EP-A-0 567 234 (JOHNSON &JOHNSON MEDICAL) * page 2, line 42 - line 46 * * page 3, line 17 - line 49 * * page 4, line 5 - line 16 * * page 4, line 36 - line 39 *	1-22	A61L31/00 A61L27/00
A,D	EP-A-0 194 192 (ETHNOR) * page 5, line 16 - line 33; claims; examples *	1-11	
A	EP-A-0 297 535 (VIPONT PHARMACEUTICAL) * page 3, line 34 - line 37 *	1-22	
A	US-A-5 037 377 (M. ALONSO) * column 3, line 7 - line 21 *	11	
A	WO-A-90 13302 (BRIGHAM AND WOMEN'S HOSPITAL)		

TECHNICAL FIELDS SEARCHED (Int.Cl.6)
A61L
A61K

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	15 November 1994	Cousins-Van Steen, G

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
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